Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2015

ÂNGELA FILIPA MACHADO FERRÃO

INVESTIGAÇÃO CLÍNICA NUMA INDÚSTRIA FARMACÊUTICA

Clinical Research in a Pharmaceutical Industry

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Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica de Ana Patrícia Rei, Gestora de Assuntos Médicos do Departamento de Investigação da Bluepharma Indústria Farmacêutica S.A. e do Doutor Bruno Gago, Professor Assistente convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Dedico este trabalho aos meus pais, ao meu marido e à minha filha.

o júri

presidente	Professor Doutor José Luís Almeida Professor Associado Convidado, Universidade de Aveiro
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agradecimentos

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palavras-chave

Ensaios clínicos, promotor, bioequivalência, *highly variable* drugs, gestão de projectos, inovação.

resumo

O presente relatório de estágio propõe-se relatar o conhecimento e a experiência adquirida durante o estágio curricular no setor de Assuntos Médicos do departamento de Investigação da Bluepharma Indústria, S.A..

Nele são abordadas as principais atividades realizadas, inerentes à condução de ensaios clínicos de fase I por parte de um promotor, nomeadamente de ensaios de bioequivalência. Neste contexto é feita uma descrição da legislação aplicável, do processo de gestão de um ensaio clínico e uma reflexão acerca dos principais desafios nesta área.

Para além disso, são também descritas atividades relacionadas com a gestão de projetos de Investigação, Desenvolvimento e Inovação, particularmente na análise de ideias de novos produtos farmacêuticos para as quais contribuí com diversas pesquisas.

Este meu primeiro contacto com a indústria farmacêutica permitiu-me integrar os conhecimentos e competências da licenciatura em Ciências Farmacêuticas com os adquiridos no mestrado de Biomedicina Farmacêutica, cumprindo um dos principais objetivos que estabeleci para mim: o do crescimento e aquisição de competências aliado ao acesso a uma diferente realidade profissional.

keywords

Clinical trials, sponsor, bioequivalence, highly variable drug products, project management, innovation.

abstract

This training report describes the knowledge and experience gained during the curricular internship at the Medical Affairs unit of the Research Department of Bluepharma Indústria S.A..

The main activities addressed are related with the conduction of phase I clinical trials by a sponsor, namely bioequivalence clinical trials. In this context, is described the main applicable regulations, the management process of a clinical trial and a reflection about the main challenges in the field.

Furthermore, are outlined the activities related with the management of Research, Development and Innovation projects, particularly the analysis of ideas of new pharmaceutical products, where I contribute with several researches.

This first contact with the pharmaceutical industry allowed me to integrate the knowledge and skills gained in the Pharmaceutical Sciences degree with those gained in the master's course of pharmaceutical medicine, fulfilling one of the main objectives that I define for myself: the growth and acquisition of skills, coupled with the access to a different professional reality.

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List of Abbreviations

AE – Adverse event

ANDA – Abbreviated New Drug Application

ASEAN – Association of Southeast Asian Nations

AUC – Area under the curve (pharmacokinetic parameter)

B2B – Business-to-business (marketing term)

B2C – Business-to-consumer (marketing term)

BCS – Biopharmaceutics Classification System

BE – Bioequivalence

CES – Ethics Committee for Health

CFR – Code of Federal Regulations

CIS – Commonwealth of Independent States

C_{max} – Maximum serum concentration (pharmacokinetic parameter)

CI – Confidence Interval

CNPD – Portuguese Committee for Data Protection

CRF – Case Report Form

CRO – Contract Research Organization

CSM – Clinical Study Manager

CSR – Clinical Study Report

CT – Clinical trial

CTA - Clinical Trial Application

CTD – Common Technical Document

CTP – Clinical Trial Protocol

DAG – Analytical and Galenic Department

EFPIA – European Federation of Pharmaceutical Industries and Associations

EMA – European Medicines Agency

EMAS – Eco- Management and Audit Scheme

EU – European Union

FDA – Food and Drug Administration

FMEA – Failure Mode Effects Analysis

GCPs – Good Clinical Practices

GLPs – Good Laboratory Practices

GMPs – Good Manufacturing Practices

HVDP – Highly Variable Drug Product

ICF – Informed Consent Form

ICH – International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IMP – Investigational Medicinal Product

IMPD – Investigational Medicinal Product Dossier

IMS - integrated management system

IRB/IEC – Institutional Review Board/ Independent Ethics Committee

KOLs – Key Opinion Leaders

MA – Medical Affairs

MedDRA – Medical Dictionary for Regulatory Activities

MFDS – Ministry of Food and Drug Safety (Korea FDA)

PI – Principal Investigator

PK – Pharmacokinetics

PM – Project Manager

QP – Qualified Person

RA – Regulatory Authority (ies)

RDI – Research, Development and Innovation

R&D – Research and development

RNEC – Clinical Trials National Register

RSABE – Reference-Scaled Average Bioequivalence

SAE – Serious Adverse Event

SM – Study Monitor

SME- Small and Medium Enterprise

SmPC – Summary of Product Characteristics

SOP – Standard Operating Procedure

SUSAR – Suspected Unexpected Serious Adverse Reaction

$T_{1/2}$ – Half- life (pharmacokinetic parameter)

TMF – Trial Master File

TPP – Target Product Profile

US/USA - United States of America

WHO – World Health Organization

1. Introduction

The present thesis was elaborated under the scope of the Master's Degree in Pharmaceutical Medicine and summarizes my experience at *Bluepharma Indústria Farmacêutica SA* since 5 January until 5 June of the current year. The curricular internship was focused on the collaboration in the Medical Affairs Unit, which is part of the Research Department of the company, mainly in the management of phase I clinical trials sponsored by Bluepharma and scientific research related to the clinical area.

In the introduction below, a brief description of the pharmaceutical industry, the company and the Research Department are presented. Then, the major regulations and requirements for conducting phase I clinical trials are outlined.

In the following two chapters the activities performed during the internship are described. The first chapter refers to the management of phase I clinical trials that was the main activity of the internship: Bluepharma's clinical trial planning, execution and finalization will be outlined. The second chapter refers to Bluepharma's management of new pharmaceutical product ideas, which is part of the Innovation Strategy of Bluepharma. The role of research for clinical information as well as its impact on the analysis of ideas of new product development projects is outlined.

Before the discussion section, there is brief chapter with the description of the training courses attended at Bluepharma during the internship.

The discussion chapter includes a reflection about the current challenges for clinical trial sponsors and for the pharmaceutical industry.

In the end, a final keynote under the conclusion section highlights the main achievements of the internship.

1.1. Internship objectives

When I decided to enroll myself in the Masters Course of Pharmaceutical Medicine, after ten years of work in a community pharmacy, my objective was to learn and gain new skills that would allow me to change my professional life. An experience through an internship in the

pharmaceutical industry seemed to me essential for achieving that goal, and some objectives were outlined.

- Understand Research, Development and Innovation in the context of a pharmaceutical industry:
    - ✓ Learn about the activities related with the role and responsibilities of a sponsor of clinical trials;
    - ✓ Learn how clinical trials can be managed by a sponsor;
    - ✓ Learn how innovation can be managed in a pharmaceutical company;
    - ✓ Understand the Integrated Quality management System, and how it is correlated with guidelines and regulations.

- Practical knowledge:
    - ✓ Manage Clinical Trials;
    - ✓ Use guidelines and regulations;
    - ✓ Gather scientific information in the clinical area;
    - ✓ Use the documental system of the company;
    - ✓ Apply the internal procedures.

- Develop soft skills:
    - ✓ Professional network;
    - ✓ Communication skills;
    - ✓ Self-confidence;
    - ✓ Teamwork.

1.2. Overview of the company

Bluepharma is a pharmaceutical company, headquartered in Coimbra and founded in 2001 by Portuguese investors connected with the pharmaceutical industry that acquired the facilities of Bayer's industrial unit and their human resources with more than 30 years of experience in the industry.

The main activities of Bluepharma are:

- Producing pharmaceutical drugs for Bluepharma and other companies;
- Research, development and registration of pharmaceutical drugs;
- Marketing of generic pharmaceuticals (1).

The company has a manufacturing site dedicated to oral solid dosage forms, approved by the most demanding regulatory authorities worldwide: US-FDA, EU-GMP, Korea FDA (MFDS), Taiwan FDA and Iran TGA.

Bluepharma is inserted in a highly competitive market, with large multinational companies. The global market of pharmaceuticals was worth about 900 billion US dollars in 2014, as it can be seen in Figure 1 (2). Furthermore, ten companies control one third of the market, six of them based in the United States and four in Europe (3).

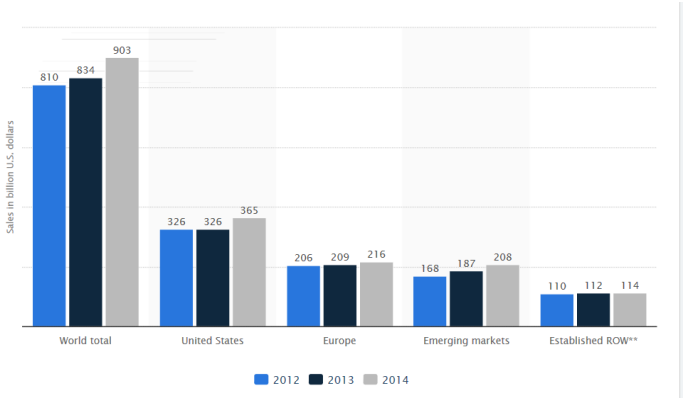

***Figure 1* – Global pharmaceutical sales from 2012 to 2014, sorted by regional submarkets** (2)

Bluepharma's mission is to deliver to the market pharmaceutical products with excellent quality at competitive prices, contributing to the national main objective of reducing the healthcare costs, streamline the expenses and improving the life quality of population.

The company always based its activity in four main principles: Innovation, Quality, Internationalization and Investment and has been building strong relations with major key players of the international pharmaceutical market with whom it established successful partnerships through B2B and B2C models ("Business-to-Business" and "Business-to-Consumer", respectively). Today, Bluepharma is also known for its R&D capabilities, marketing expertise, lean operational principles, economy of scale, and quality standards. (1) A competitiveness driver of Bluepharma is its internationalization strategy by exporting 82% of the total production to more than 30 countries, mainly US, Europe, Australia, Russia and CIS, ASEAN, South Korea, China and Latin America. Furthermore, the company has offices in Angola and Mozambique and local agents in China, USA, Colombia, Venezuela and Brazil (4).

Bluepharma is committed to exceed the costumer's expectations and to ensure the quality of the manufactured medicinal products, respecting the environment as well as safeguarding the working conditions of its employees. For that reason, Bluepharma implemented an Integrated Quality and Environmental Certification program according to the Norms NP EN ISO 9001, NP EN ISO 14001, OHSAS 18001, and EMAS and complies with EU and FDA GMP guidelines.

Over the time, Bluepharma's Group has been growing and expanding its research activities and capabilities. Over the years, Bluepharma has been changing from a traditional contract manufacturing organization to a company that promotes innovation, with several projects in its pipeline, both generic and innovative medicines.

Besides, Bluepharma has ten subsidiaries promoting a robust chain value for the discovery and development of innovative pharmaceutical products and technologies (5) (6). The relation between them is outlined in the figure 2.

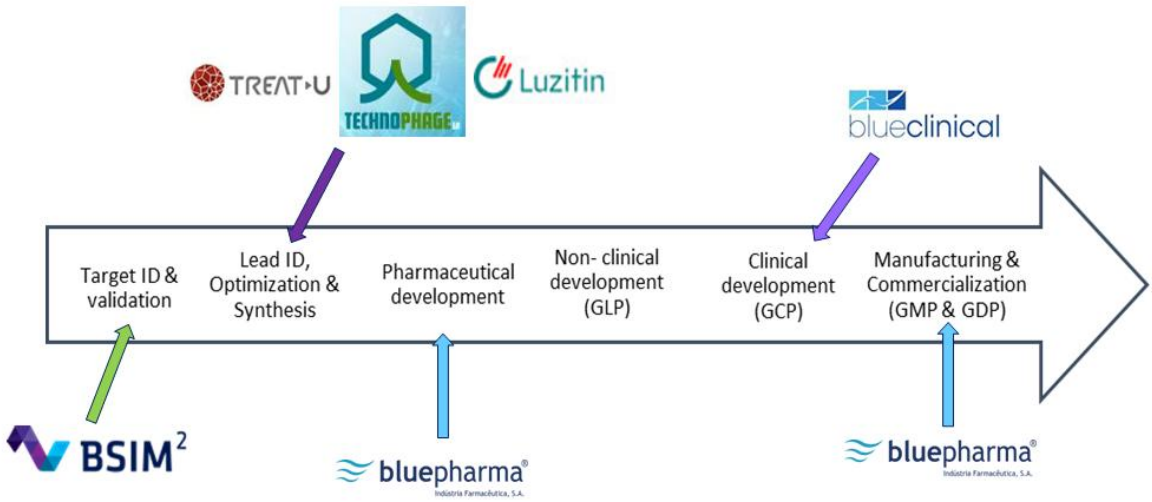

***Figure 2* - Bluepharma's Subsidiaries and Value chain.** Adapted (7)

Below is a summary description of some of them:

- ***Bluepharma Genéricos:*** dedicated to the marketing of high quality generic medicines, with 72 generic medicines in its portfolio.
- ***BSIM²:*** dedicated to computational methodologies to boost discovery of new drug candidates and lead optimization.
- ***TreatU:*** dedicated to the development of targeted nanotechnology-based platforms for the delivery of drugs used in oncology (8).

- ***Luzitin:*** focused on the development of new technologies for use in oncology and dermatology.
- ***Blueclinical:*** the first Contract Research Organization (CRO) in Portugal who has a unit for phase I clinical trials. It promotes R&D by supporting institutions and companies in the development of their projects and the activity of clinical research sites that conduct studies with drugs and medical devices. Blueclinical is the partner of choice of Bluepharma for conducting phase I clinical trials (9).
- ***Technophage:*** dedicated to R&D of new molecules (early-phases) in therapeutic areas like neurology, metabolic disorders, infections and immunology (10).

1.3. Bluepharma's Research Department

The Pharmaceutical Industry is one of the industries that spend more in R&D, with a total spent, in the last 10 years, over 1.2 trillion US dollars. Data from EvaluatePharma® shows that only in 2014, the pharmaceutical industry invested about 141 billion US dollars in R&D (11).

Bluepharma's Research department has a defined mission that consists in fully supporting Bluepharma's innovation pathway, through the conception, management and execution of research projects with the aim of creating truly unique medicines that are patient-centered, safe and effective, thus supporting the company's competitiveness. It also provides scientific support to other departments and associated companies.

This mission can be achieved using the following values:

- ***Innovation:*** by continuously asking what can be done differently to create value;
- ***Excellence:*** through demanding more of ourselves than anyone else and going beyond what is expected;
- ***Efficiency:*** by managing resources smartly and focusing on activities that create value;
- *Teamwork*: because the best ideas come from sharing experiences and working together with others;
- ***Ethics and Integrity:*** by being honest, reliable and complying with all applicable laws and regulations.

The Department is divided in 3 main units that can be seen in the Figure 3. Their main roles are the following:

1. ***Research Unit:*** dedicated to research projects, both for technology development and nonclinical studies;
2. ***Innovation Strategy Unit****:* which includes the management of Research, Development and Innovation (RDI), the internationalization strategy and of non-dilutive funding & valuation of technology;
3. ***Medical Affairs Unit*****:** responsible for the clinical development of innovative and generic medicines.

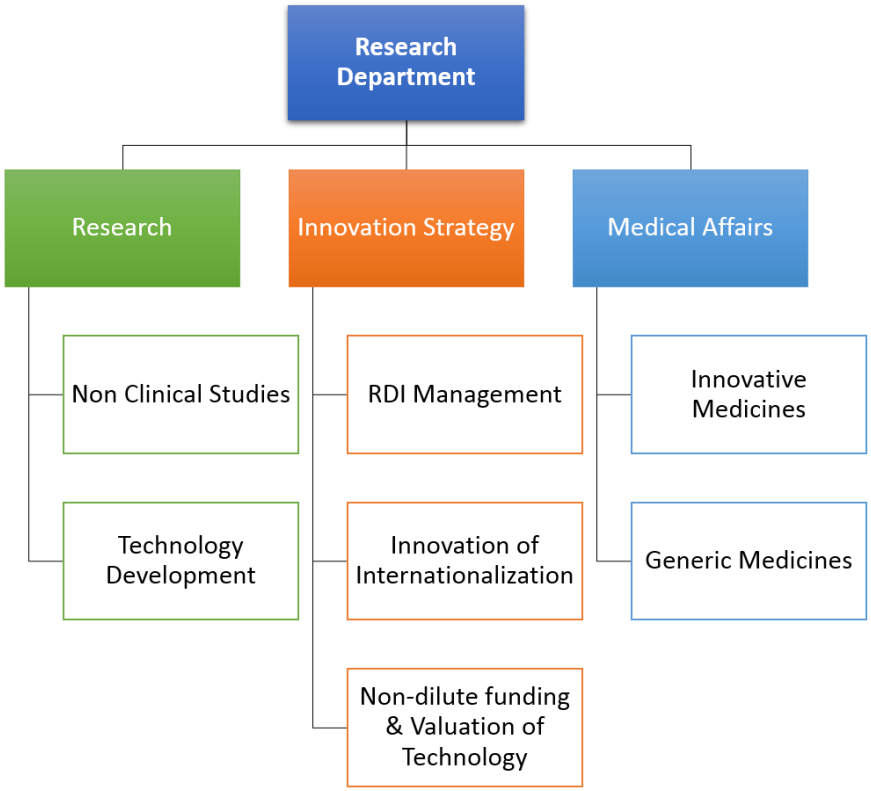

Figure 3 **- Organization chart of Research Department**

In the chapters 2 and 3 of this report, the activities of the two last units will be described in more detail.

1.3.1. Innovation Strategy

It is known that Pharmaceutical Companies need to find mechanisms to develop and to preserve its competitive advantage, doing more with less. They need to work smarter and innovate faster, which is not a simple task to perform. The vital role of R&D is to sustain and help growing a business through innovation. The R&D activities are an investment in the future of a company because, even in long-term, they create value.

By being inserted in a highly competitive market, Bluepharma considers innovation as one of the pillars of its development strategy. The innovation can be applied in the development of new products, new processes, new organizational and marketing models, bringing a competitive advantage for the company.

In 2012, Bluepharma implemented the Portuguese Norm NP 4457:2007 (*Management of RDI Systems)* in order to optimize its innovation strategy, the management of RDI projects and improving its competitiveness. That year Bluepharma obtained the certification by an accredited organization, APCER.

The NP 4457:2007 defines the requirements for a RDI management system and is based on the management of three main interfaces:

1. Technologic interface;
2. Organizational interface;
3. Market interface.

The management of interfaces allows the collection, through different sources, of information from the external environment, which leads to the gain of knowledge by the company (12). For that purpose several activities can be performed, for example:

- Perform scientific and technological monitoring, technological cooperation and technological foresight;
- Identifying activities and tools that can enhance the creativity within the company to ensure the production of organizational knowledge;
- Analyze the external environment, including potential customers and new markets.

Internally, several persons are appointed to perform the monitoring of the external stakeholders. The knowledge gained with these activities can lead to the generation of ideas and identification of opportunities (12).

According to the Portuguese regulation NP 4457:2007, a system for ideas management and opportunities assessment should be implemented in order to select the best projects to be

developed, which must be consistent with the innovation strategy of the company. The RDI projects must also be managed in such a way that results can be evaluated with the purpose of understand which was the beneficial impact for the company (12).

One limitation of R&D activity is that it can be managed but its outcomes are not (13) (14). However, when the management is efficient, it leads to a lot of benefits:

- Better adaptation face to external/ internal changes;
- Close monitoring in order to maximize the investment for a particular risk;
- Identification of dependencies between projects, which turns possible the maximization of resources;
- Well defined strategies (14).

Below, in Figure 4, is a scheme that represents the relationship between interfaces management and innovation according to the Portuguese regulation NP 4457:2007.

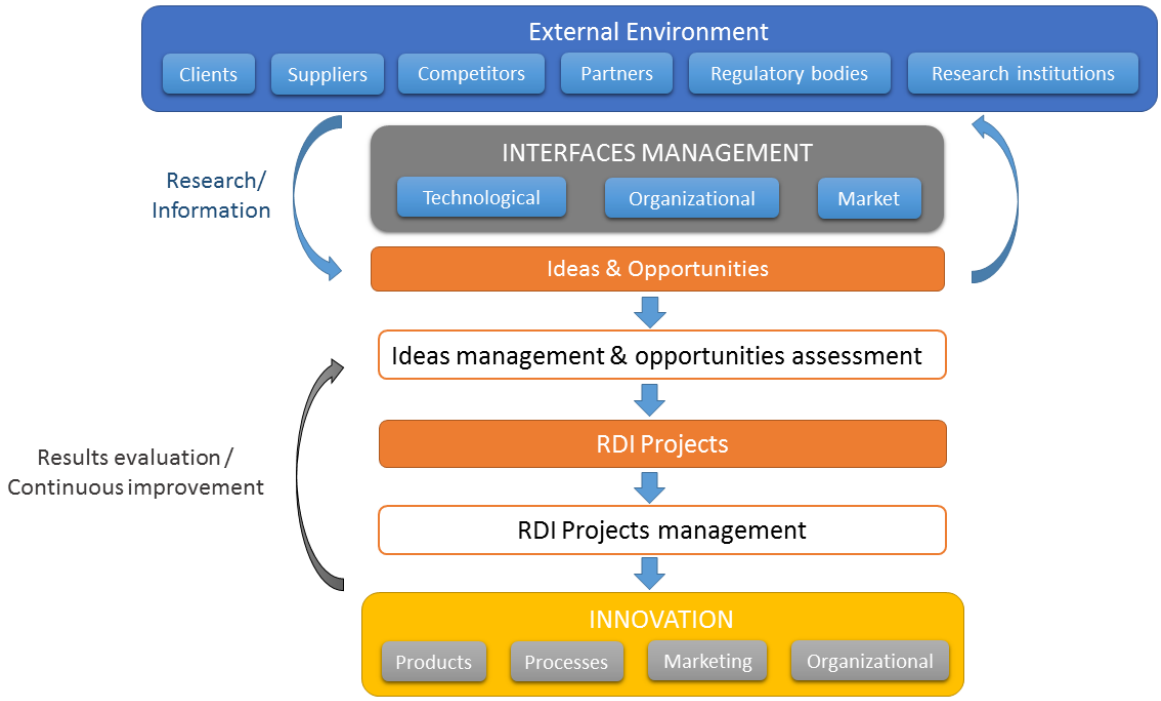

***Figure 4* - The relationship between interfaces management and innovation.** Adapted (12)

In the second chapter of this report, Bluepharma's process for managing RDI projects (namely, Bioequivalence Clinical Trials) will be described and in the third chapter a detailed description of how Bluepharma performs the management of ideas and opportunities will be made.

1.3.2. Medical Affairs

Recently, Bluepharma gain a new skill, sponsoring phase I clinical trials (CT) for both generic and innovative products. In order to support this new activity, a new dedicated Medical Affairs (MA) unit was created within the Research Department.

The main responsibilities of the MA Unit at Bluepharma are:

- Manage all Phase I clinical Trials sponsored by Bluepharma;
- Prepare Clinical Trial applications;
- Manage internal and external communications regarding all clinical trials sponsored by Bluepharma;
- Ensure the compliance of all the applicable requirements and regulations that need to be fulfilled in order to be a sponsor;
- Support scientific research in the clinical research area for internal projects.

At Bluepharma, the development of a new pharmaceutical product is divided in several phases as shown in the Figure 5, below. The conduction of a clinical trial corresponds to the phase III of the overall project. Each Clinical trial is managed as a single RDI project as described in chapter two.

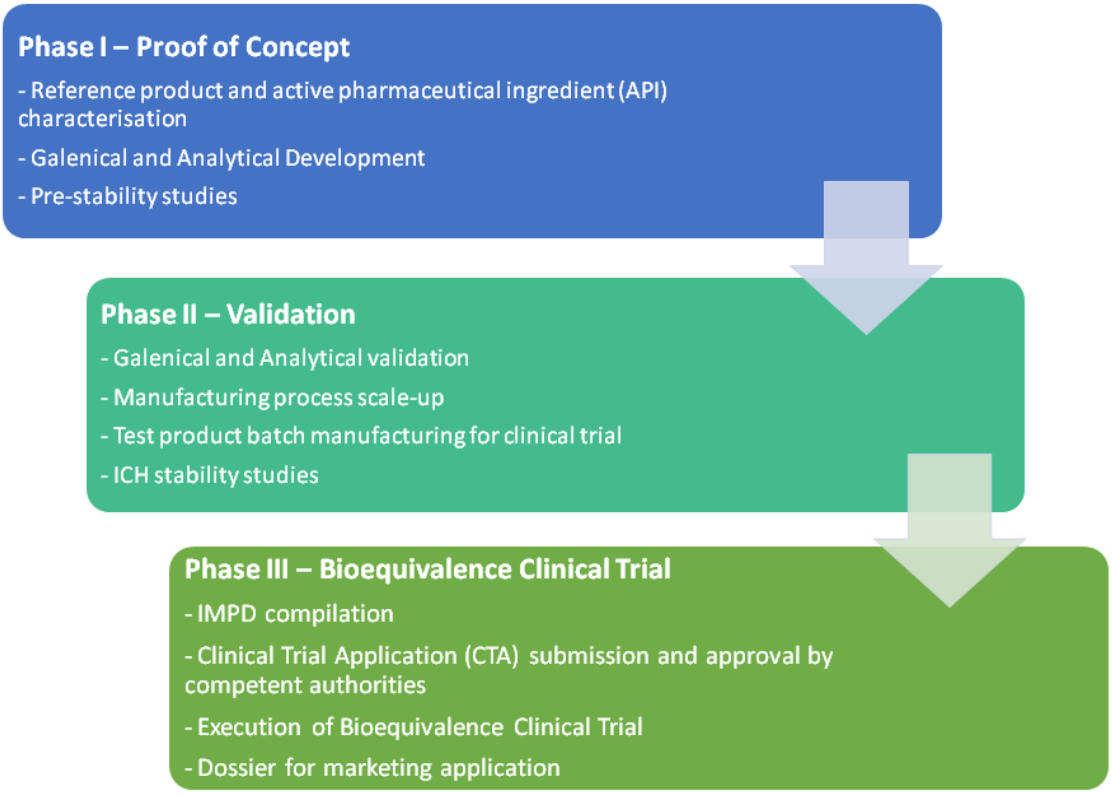

Figure 5 **– Main steps for the development of a new generic product at Bluepharma**

Before explaining how phase I clinical trials are managed at Bluepharma, the main legislation and requirements for conducting CTs as well as some particular features of evaluating bioequivalence (BE) and the special case of High Variable Drug Products (HVDP) will be outlined.

2. Clinical Trials Requirements: Regulations & Guidelines

The Pharmaceutical Industry is extremely regulated. It is mandatory that all the legal requirements are fulfilled in order to achieve the marketing authorization from the regulatory authorities for each generic or innovative product.

In order to facilitate the process and harmonize the requirements for the submission of a marketing application of medicinal products in different regions, the regulatory authorities of Europe, Japan and United States met with pharmaceutical industry representatives. The result (in the year of 1990) was the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which has been developed guidelines and tools to achieve the harmonization objective. For the ICH regions and for all medicines (in the United States is not mandatory but it is strongly recommended by Food and Drug Administration), the submission of a marketing application is made by submitting a Dossier, the Common Technical Document (CTD), which comprises all the information about quality, efficacy and safety of the product. That information is organized into 5 modules, as shown in the Figure 6.

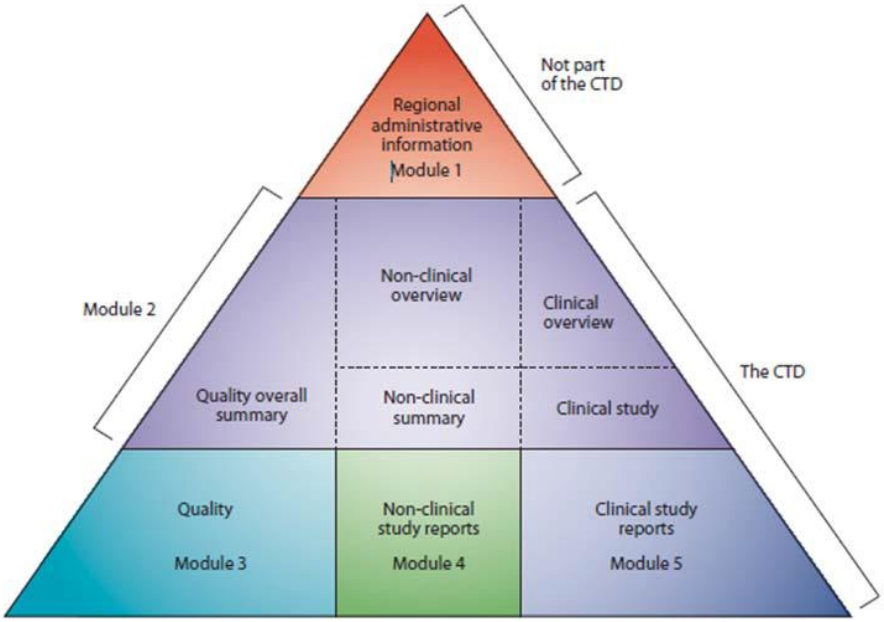

Figure 6 **- The CTD modular format** (15)

Module 1 has administrative information, which is region specific. Modules 2 to 5 are common to all ICH regions:

- Module 2- CTD summaries
- Module 3- Quality information
- Module 4- Non clinical study reports
- Module 5- Clinical study reports

The module 5 contains the clinical information about the medicinal product. In the case of generic medicinal product, the non-clinical and clinical information that supports the safety and effectiveness of the product is not required, as it has already been submitted by the marketing holder of the reference product. The clinical trial (CT) required is the Bioequivalence (BE) clinical trial.

Good Clinical Practices (GCPs)

As stated in the Guideline E6 of ICH, Good Clinical Practices are "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible" (16). The main objective of the guidance is: "...to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions" (16).

Conducting clinical trials requires authorization from the competent authorities and the favorable opinion of an Independent Ethics Committee (IEC). In Portugal, besides the approval from IEC, the conduction of the clinical trial has also to be approved also by the Committee for Data Protection (CNPD) and Infarmed (National Authority of Medicines and Health Products).

According to ICH Guideline E6, for conduction of a clinical trial an experienced team has to be gathered. The different players are schematized in Figure 7.

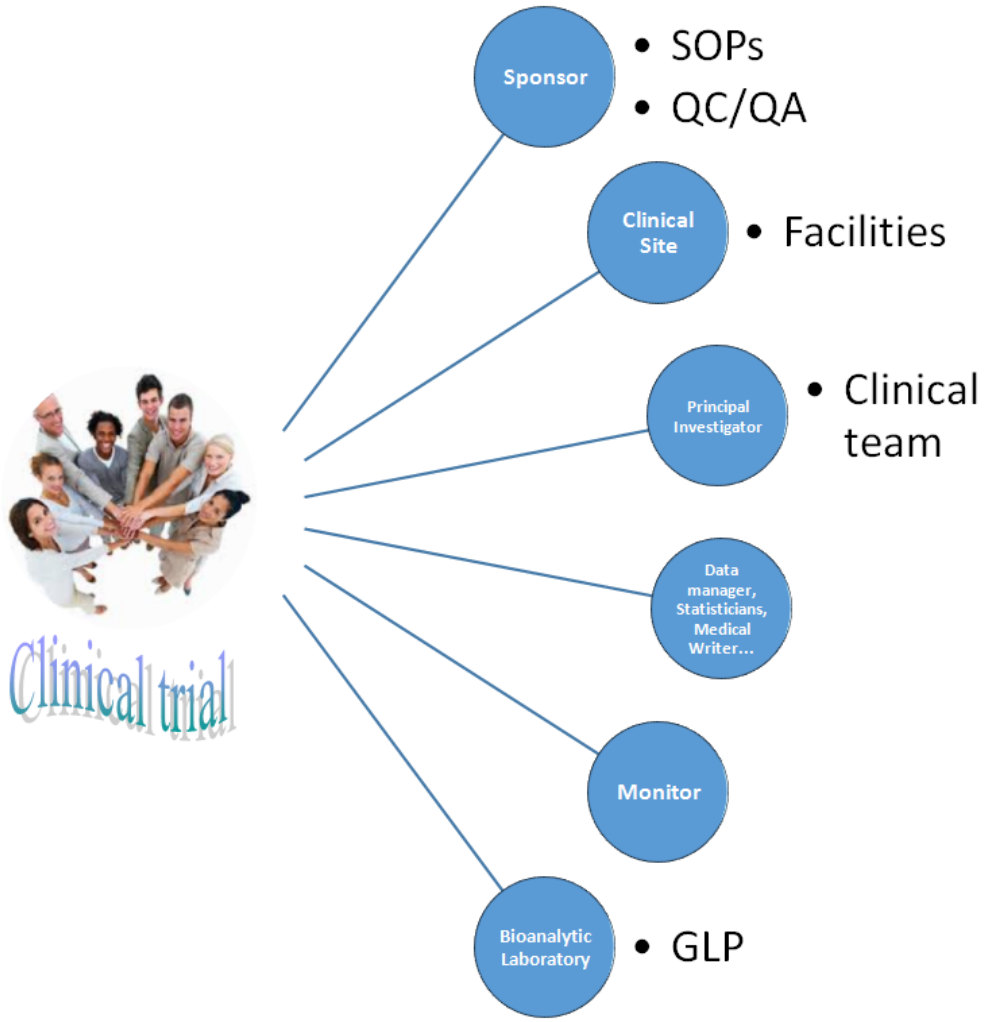

Figure 7 **– Entities involved in Clinical Trials**

Their main responsibilities, according to the same guideline, are described below.

- **Sponsor**

  The Sponsor is the "individual, company or institution which takes the responsibility for the initiation, management, and/or financing of a clinical trial." (16) As the data resulting of a clinical trial must be generated, recorded and reported in compliance with the protocol, the GCPs and the applicable requirements, the sponsor has to ensure the quality of the CT by implementing measures for its control and assurance. Other main responsibilities of the sponsor are:

  - Select the clinical site (which depends on the type of study);
  - Prepare and submit the required documentation for study approval;

- Propose the principal investigator and provide him with all the known data about the Investigational Medicinal Product (IMP) and necessary supplies to the efficient conduct of the trial;
- Ensure that IMP is manufactured according to the Good Manufacturing Practices (GMPs) and labeled in a manner that protects the blinding (if applicable);
- Retain all the specific essential documents pertaining to the trial;
- Notify to regulatory authorities and to Institutional Review Board/Independent Ethics Committee (IRB/IEC) all concerned findings that could adversely affect the safety of subjects.

Although any or all of its roles may be transfer to a CRO, the final responsibility for the CT always relies in the sponsor. All the parties involved in the CT must be aware of their responsibilities. As such, a written agreement where all the responsibilities, and with the parties involved, should be comprehensively defined. The sponsor must maintain a good line of communication to ensure that all the obligations are being met (16).

- **Principal Investigator**

The Principal Investigator is the responsible person, at the clinical site, for the conduct of the CT. He must have the necessary qualifications for performing its duties, which are:

- Have the appropriate number of qualified staff and the conditions to conduct the CT properly and with safety;
- Conduct the clinical trial in compliance with the clinical trial protocol, the GCPs and the applicable regulatory requirements;
- Be responsible for IMP accountability at the trial site (or assign this responsibility to a pharmacist);
- Ensure the accuracy, completeness, legibility and timeless of the data reported to the sponsor in the Case Report Forms (CRFs) and in reports;
- Make directly available, when required, the CT related records;
- Obtain the Informed Consent and provide to participants all the information needed;
- Provide medical care to the subjects;
- Report all Serious Adverse Events (SAEs) to sponsor (16).

- **Clinical site**

The clinical site is the location where the clinical trial will be conducted. The clinical trial facilities must be suitable for the needs of the trial and must have the adequate resources (16) (17). The associated staff must be trained in GCPs and comply with them.

- **Monitor**

  The monitor(s) takes part in quality control. Its activities are appropriate in extent and nature to the features of the CT (purpose, design, complexity, end-points, as well as the risk posed by the IMP), and aim to assess the compliance with the requirements and to identify potential or existing gaps in order to prevent and/or correct them. The monitor works closely with the sponsor for ensuring that the clinical trial has being performed according to the protocol, Standard Operating Procedures (SOPs), GCPs and applicable legislation. Furthermore, the monitor verifies:

  - The investigator's qualifications and experience in GCPs;
  - The conditions of the facilities and if they are adequate to the conduct of the study;
  - If the IMP is supplied according with the clinical study protocol and if the documents related with the IMP are signed and updated;
  - If the CRFs are properly filled and if the collected data is reliable, complete and in accordance with source documents.

  After the monitoring visits, the monitor elaborates a monitoring report, containing a summary of what is examined during the visit, the problems detected and the preventive and corrective actions that must be undertaken if needed, and share it with the sponsor (16) (18).

- **Auditor**

  The auditor is part of the quality assurance and is an individual independent from the sponsor. The quality assurance activities are systematic and their regularity depends on the risk assessment of the clinical trial. The auditor examines the trial activities to ensure that they are performed according to the clinical trial protocol, SOPs, GCPs and all the regulatory requirements. The audits are focused on the personnel responsibilities, the qualifications and training of the clinical team, the IMP supplies and procedures, the essential documents, computerized systems and, basically, in all the activities that could affect the principles of GCP: subjects welfare and data integrity (16) (18).

- **Bioanalytical Laboratory**

  The Bioanalytical Laboratory analyzes the biological samples (urine, plasma, etc) collected from patients or healthy volunteers participating in CTs. In a Bioequivalence study the bioanalytical analysis consists in the quantification of the drug product or its metabolites in the biological samples. As the importance of this data, these laboratories must be certified in Good Laboratory Practices (GLPs).

In addition to GCPs and depending on the region, the conduction of clinical trials has to comply with other guidelines: Eudralex Volume 10 published by European Commission or several "Guidance for Industry" published by Food and Drug Administration (FDA).

European Regulations

- **Portuguese Law No 21/2014, of 16 April**

  This law was recently approved with the goal of increasing the number of clinical research activities and it is a transposition of the European Directive No 2001/20/EC which regulates clinical research activities on human medicines, EU Directive No 2007/47/CE on medical devices and also GCPs. The main objectives of this law are:

  - To simplify the approval procedures for CTs in order to make the legislation more competitive compared with other countries;
  - To strengthens the role of ethic committees;
  - To clarify the responsibilities of sponsors, principal investigators and monitors;
  - To create favorable conditions for the disclosure of clinical trials;
  - To create the National Registry Platform for Clinical Studies, an internet platform that able the registration of clinical trials, improves the interaction between the stakeholders and advise the general public about what are clinical trials;
  - To create conditions in the medical career that encourages professionals to proactively perform clinical research activities;
  - To create an investment fund for clinical research (19).

  One of the most important measures was the shortening of the deadlines (for 30 days) of the approval of clinical trials for both National Ethics Committee for Clinical Research (CEIC) and Portuguese Committee for Data Protection (CNPD).

- **Regulation EU No 526/2014**

  In Europe, a new Regulation, the No 536/2014, repeals the Directive 2001/20/EC and aims to:

  - Simplify the current rules, maintaining the same high standards of patient's safety;
  - Create a positive environment for conducting clinical trials within the EU;
  - Increase the transparency on clinical trials information through the use of the "EudraCT" website;
  - Regulate the principles for clinical trials performed outside the EU but being included in marketing applications inside the EU;
  - Simplify the procedure for safety reporting (20) (21).

  "EudraCT" is the EU Portal and Database developed by European Medicines Agency (EMA) that provides several advantages:

  - Facilitates the clinical trial application, especially for multinational clinical trials, due to a single Clinical Trial Application (CTA) for all CTs performed in the EU;
  - Makes the assessment of CTA by the authorities easier;
  - Makes easier the accession to the information about clinical trials by the general public.

  The registration in the EudraCT portal is mandatory for the assessment of a CTA. Aiming the increase of transparency, up to one year after the end of a clinical trial, sponsors have the duty to submit a summary of the outcomes of all CTs conducted in EU (21).

  The principles and procedures for GCP inspections are another topic that lay down in this regulation. Regulation 536/2014 entered into force on 16 June 2014 but it will only be applied on May, 2016. Then, the Directive 2001/20/EC will be repealed but there is a transition period of three years (21).

- **Commission Directive 2005/28/EC**

  The Directive 2005/28/EC lays down the principles of GCPs regarding investigational products for human use and also the requirements for the authorization of the manufacturing and importation of such products.

- **Commission Directive 2003/94/EC**

This Directive regulates the main principles of GMPs applicable to human medicines and IMPs.

US Regulations

- **Title 21 of Code for Federal Regulations (US)**

  For companies intending to market their products in US, the FDA regulations must be fulfilled. The regulations concerning the conduction of CTs are included in Title 21 of the Code of Federal Regulations (CFR). As these regulations are in some ways different, in a number of points, from those in EU, the pharmaceutical companies have to take into account these discrepancies when they want to market a product in the two regions (22).

3. Clinical Trials to investigate Bioequivalence

Bluepharma develops mainly generic medicines and the majority of the clinical trials sponsored by Bluepharma are Bioequivalence trials. A generic medicinal product is a product comparable to an innovator (the reference product) since it has the same qualitative and quantitative composition in terms of the active substance, pharmaceutical form, quality and intended use. In order to be comparable and interchangeable the generic and the reference have to be bioequivalent, that is, according to the EMA Guideline on the Investigation of Bioequivalence, "two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailability (rate and extent) after administration in the same molar dose lie within acceptable predefined limits" (23). Two drug formulations (test and reference) are bioequivalent when they yield, in the same study conditions, equivalent blood levels of active substance. For that, a bioequivalence clinical trial is performed (23) (24).

According to ICH Guideline E8 (General Considerations for Clinical Trials), Clinical trials to assess bioavailability and bioequivalence of medicinal products are a type of phase I clinical trials. They are human pharmacology studies, with a design that allows studying pharmacokinetics (PK) without the interference of internal or external factors (they are highly controlled). In this kind of CTs the PK parameters are the study endpoints (25). They have non-therapeutic objectives and are usually conducted in healthy subjects, except for that cases which is not ethical to include healthy persons (e.g. studies with cytotoxic drugs).

The limits referred in the guideline differ according to the type of product. Usually, they are 80.00 to 125.00 for the geometric mean ratio for C_{max} and AUC (outlined in Figure 8) (26), with a 90% confidence interval (CI). Guidelines and regulations recommend the use of an average bioequivalence statistical approach when investigating bioequivalence (23).

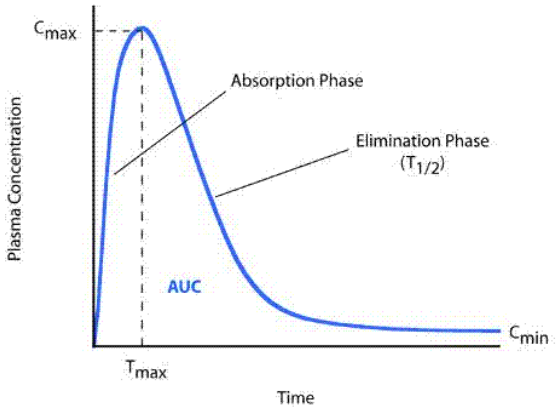

***Figure 8*- AUC curve** (26)

There is a standard design for the CT on investigation of bioequivalence:

- Randomized;
- Two-period;
- Two-treatment (A and B: one is the reference and the other is the test);
- Two-sequence single dose crossover.

Periods are separated by a wash-out period, normally at least 5 times the $t_{½}$ (elimination half-lives) of the substance, in order to eliminate the carryover effect[1] (27).

This design is called a 2x2 crossover design.

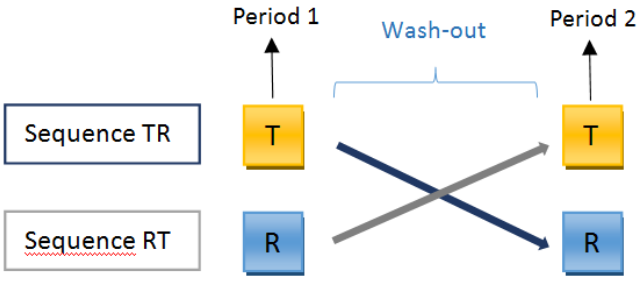

***Figure 9* - 2x2 Crossover Design**

[1] The elimination of the carryover effect certifies that when the second period begins the amount of drug in the blood is not quantifiable (the drug concentration is below the lower limit of quantification of bioanalytical analysis).

However, this design is not suitable for drug substances comprising long half-lives and for highly variable drug products. Consequently, BE studies can be performed with other designs. For example, for drug substances with a long elimination half-live, a parallel design may be used; or for highly variable drugs, replicate designs.

Usually, the BE studies are conducted in a fasted state because this is considered the most sensitive condition to detect differences between treatments. However, when the Summary of product Characteristics (SmPC) recommends the use of the drug product only in fed state, then the study must be conducted accordingly. If this is the situation, a high fat meal (50% of the total caloric content of the meal must be fat), with approximately 800 to 1000 kcal, is given to study subjects (23).

Although, in US, the FDA usually recommends the investigation on bioavailability/ bioequivalence to be determined by two studies: one in fed and another in fast state.

When two or more strengths of the product are marketed, the need to perform tests in the additional strengths depends on the linearity of the PK parameters. In the case of PK linearity (when the increase in AUC is proportional with the dose) it is possible to perform only one BE trial (with only one of the strengths – the highest one is the recommended, however other strengths are accepted when justified, e.g. subjects safety) and an *in vivo* waiver could be used to extrapolate the results to other strengths. In this situation, an *in vitro* dissolution test is always required for waiving (23).

3.1. Bioequivalence of Highly Variable Drug Products (HVDP)

Drug substances can be categorized by the Biopharmaceutics Classification System (BCS) according to their aqueous solubility and intestinal permeability, as it can be seen in Figure 10. These characteristics have many implications in the PK parameters of the drug, namely in the rate and extent of absorption, when incorporated in oral pharmaceutical forms (28).

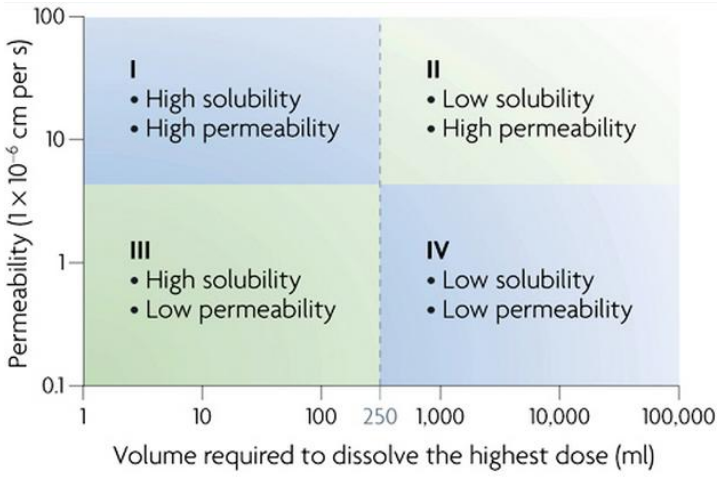

Figure 10 **- Biopharmaceutical Classification System (BCS): characterization of drugs based on solubility and permeability measures** (29)

Several pharmaceutical drug products belong to classes II and IV (low aqueous solubility/low permeability and low aqueous solubility/high permeability). These drugs present a high lipophilicity and, usually, an extensive pre-systemic metabolism (fist-pass metabolism) (30) (31), which results in a low bioavailability and high variability on the disposition pattern, leading to a high failure rate in BE studies (32).

By definition, HVDP are drugs whose within-subject variability for AUC or C_{max} (the parameters evaluated in BA studies) is higher than 30% (23). Figure 11 (30) represents the limits of 80% and 125% on the geometric mean ratio in a BE clinical trial between test and reference with 90% CI, and compare the results of a drug presenting a normal variability and one highly variable drug. The green and red bars represent the 90% CIs. As it can be seen, Drug A (normal variability) meets the BE limits, whereas Drug B (highly variable) does not. CI is influenced by the sample size, which must be increased to prove the BE in these cases.

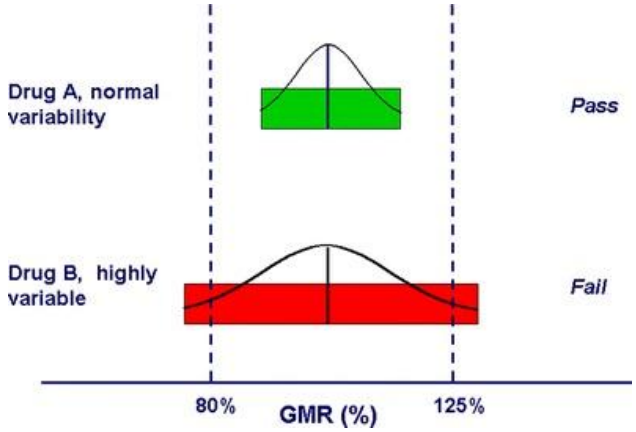

***Figure 11* - Limits for accepting BE** (30)

To solve this problem, other designs may be required, namely replicate designs, in order to decrease the sample size while achieving an acceptable result in the BE clinical trial (30). In these designs, the reference and/or the test product are given twice to the same subject. So, not only the *within-subject variability* could be evaluated but also *the within-subject variability per treatment* (also called *subject-by-formulation interaction).* Examples of replicate designs are described below:

a) **Full replicate design (four-way crossover)**: in which test and reference are given twice to the same subject (Figure 12) (33).

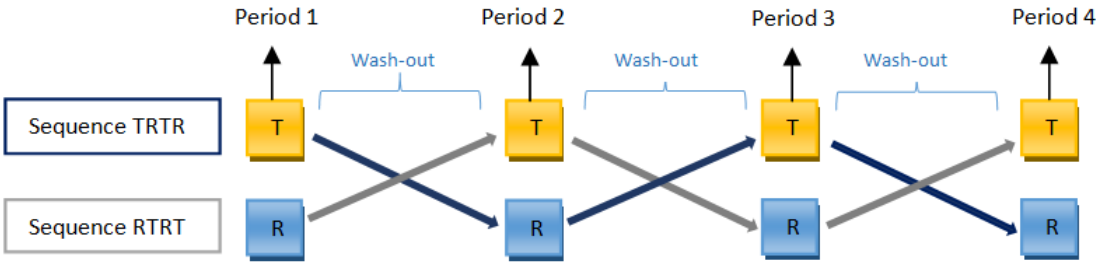

***Figure 12* - Full replicate design: four-way crossover.** Adapted (33)

b) **Partial Replicate design (three-way crossover):** in which one of the treatments (in the Figure 13 (33) below, the reference) is given twice to the same subject.

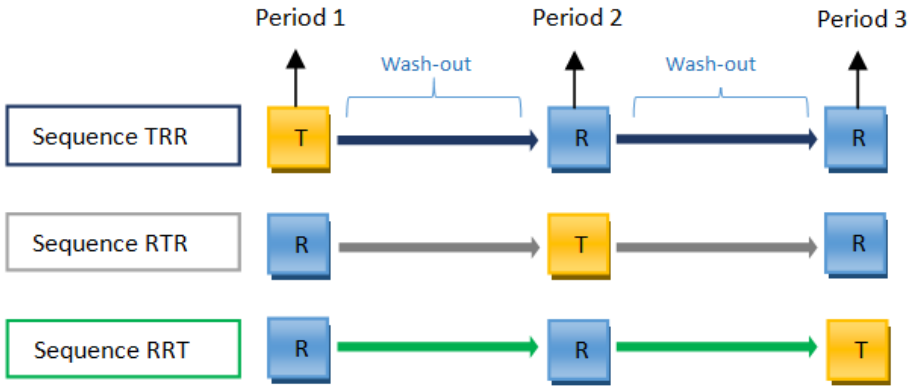

***Figure 13* - Partial replicate design: three-way crossover.** Adapted (33)

When using replicate designs in a BE clinical trial, other statistical approach than the average BE can be used: a *reference-scaled average bioequivalence approach* (RSABE), which adjusts the BE limits by scaling to the within-subject variability of the reference, maintaining the 80% and 125% as limits for BE acceptability (27) (30) (34) (35).

The case of HVDP is not a simple question since EMA and FDA look at it differently, has shown in the Table 1.

***Table 1* - EMA and FDA outlook on BE clinical trials for HVDP**

EMA	FDA
The *statistical approach* considered is the *average bioequivalence with expanding limits* (33) (23).	The statistical approach should be a *reference-scaled average bioequivalence* (36).
Accepts *replicate designs*. (3-period or 4-period crossover).	Accepts *replicate designs* (3-period or 4-period crossover).
Accepts a *widening of the C_{max} limits* with a maximum for interval widening of 69.84 to 143.19 of geometric mean ratio for C_{max} . (If the difference in C_{max} does not represent clinical relevance and if it is not due to outliers) (23).	The interval of acceptance is always 80,00 to 125,00% of the geometric mean to AUC and C_{max} (31). However, the RSABE approach adjusts the BE limits (AUC and/or C_{max}) according to the within-variability of the drug (33).

The possibility to widen the acceptance interval *is not applicable to AUC*. For AUC, the range is the same of the other type of substances: 80.00 to 125.00% (16).	The use of other (secondary) point estimate to being between the limits of 80,00 to 125,00 %, decreases the advantage of using the reference-scaled approach because an increase in the sample size will be required anyway (33).

When submitting an Abbreviated New Drug Application (ANDA) for FDA or a Generic Application for EMA, all these aspects must be taken into account. One of the main risks when developing a generic product resides in the failure of the BE study, as it may compromise the completion of the project. During the internship, I made a report about HVDP regarding the design of BE studies for this type of drugs and the opinion of the regulatory authorities on the matter.

4. Managing Clinical Trials at Bluepharma

As mentioned before, at Bluepharma, a clinical trial is a phase III project and its management is performed by the Medical Affairs Unit. As a sponsor of phase I clinical trials, the company must ensure the proper conduct of the CT and that all regulatory requirements are in place and fulfilled. For that reason, the Medical Affairs Unit elaborated all the necessary internal documentation (Standard Operation Procedures – SOPs), which includes a main SOP that defines Bluepharma's specific responsibilities as a sponsor (Table 2), enumerates the internal human resources needed and the potential outsourced services involved as well as their main functions (37).

***Table 2*- Bluepharma's usual main responsibilities when sponsoring clinical trials**

Specific responsibilites of Bluepharma as a sponsor		
- Selection of CRO and/or other entities (PI, Monitor, Bioanalytical Laboratory, Clinical Site...); - Select the monitor and the auditor for quality control (QC) and quality assurance (QA); - Obtain the CT insurance; - Prepare, revise and submit (or delegate the submission) of the required **documentation** the CTA;	Ensure, regarding IMP: - Manufacture, packaging alnd labeling; - Release by the Qualified Person; - Shipment; Control the distribution, return and destruction;	- Disseminate all the necessary information to investigators; - Evaluate and report serious adverse events (SAEs) to the regulatory authorities; - Adequately monitor the clinical study; - Initiate, withhold or discontinue the CT as required.

According to the main SOP, the manager designated for this type of projects is the Clinical Study Manager (CSM), who has the responsibility of ensuring the planning, execution and follow-up of the tasks related to clinical trial projects.

According to the Norm NP 4457: 2007, each project has to be managed and for that reason a Project Manager is appointed internally. At Bluepharma, and as can be seen in Figure 14, a CT has three main phases:

1. **Start-up & planning**

To support the management, Bluepharma implemented several forms, enumerated below, to be completed when planning a project:

- ***The Project Plan Form:*** that comprises the project main scope and objectives, the selection of the team, the necessary resources, the measures to ensure intellectual property, etc.
- ***The Communication Plan Form:*** where the appropriate communication plan between the several stakeholders of the project is defined;
- ***The Risk assessment Form (Failure Mode Effects Analysis (FMEA) based)[2]:*** to perform the identification and assessment of the risks associated with the project;
- ***The Follow-up plan Form:*** where the stages of the project are defined (with timelines) in order to facilitate the management and to check the compliance with the milestones.

A Gantt chart can also be used for the management of the milestones, deadlines and resources needs.

2. **Execution, monitoring and control**

After the planning phase, the execution phase starts with a kick-off meeting, with all the team members in order to explain:

- The scope of the project;
- The activities and responsibilities of each person;
- The main timelines;
- The main objectives that must be accomplished.

[2] FMEA is the most used method to assess the risks of a project in pharmaceutical industry, but it is used in others industries either. According to FMEA, the risks are classified as their severity (if a failure happens, what will be the effect in the overall outcome?), probability of occurrence (how likely is a failure to occur?) and detectability (how detectable is the failure? Which mechanisms does the company have to detect the failure if it occurs?) (47).

At each milestone, intermediary results are monitored and assessed and, if applicable, preventive and corrective actions are implemented in order to achieve the final results.

3. Assessment of the results & project close-out

At the end of each project a final report is completed in order to evaluate the overall project accomplishment (e.g. if the timelines and the costs were achieved as expected). With each project new lessons can be learned in order optimize future projects (12).

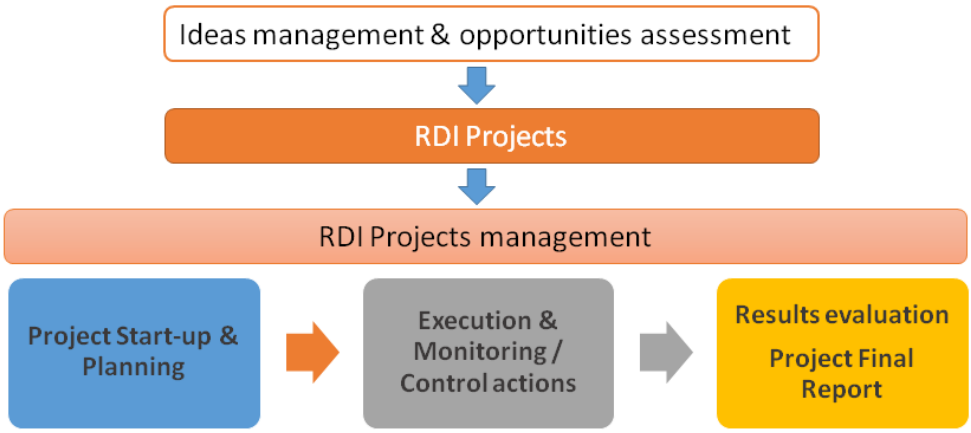

***Figure 14* – RDI project management process at Bluepharma.** Adapted (12)

Figure 15 represents the main steps to be managed by the CSM when conducting phase I CTs sponsored by Bluepharma and the internal and external parties involved. In the following sections, they are described, as well as my contributions during the internship.

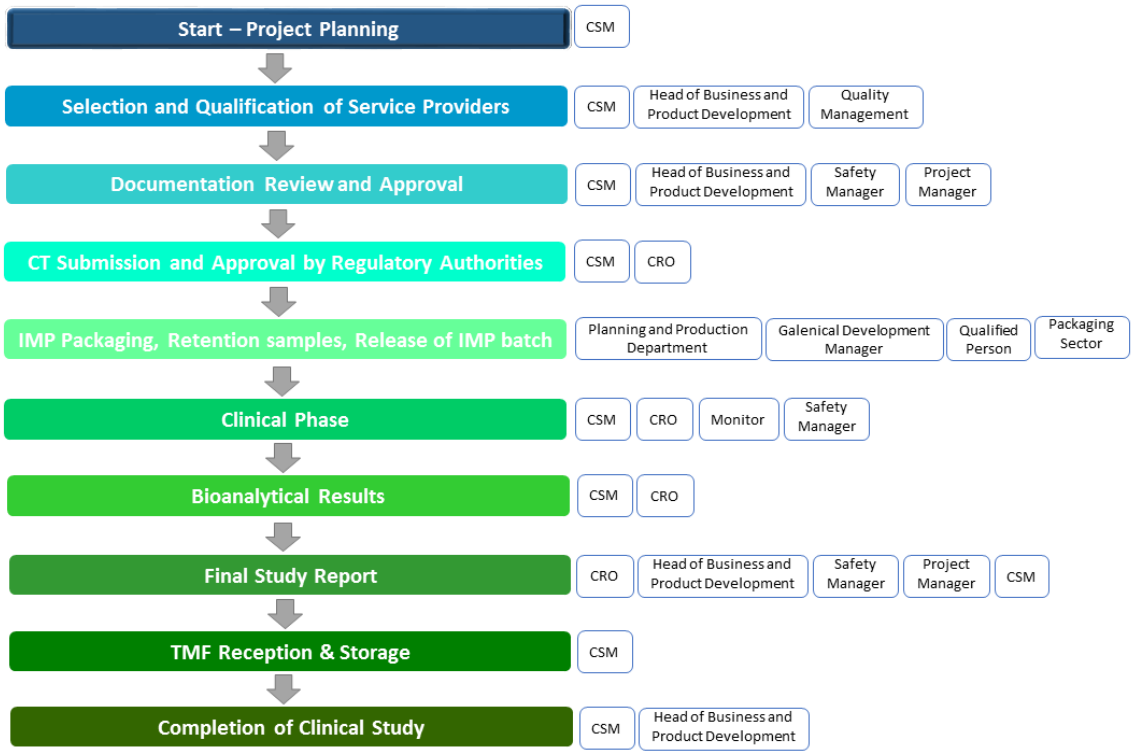

Figure 15 **– Process of conduction a Clinical Trial Project at Bluepharma and internal and external parties involved**

4.1. Planning a Clinical Trial

When planning the CT, the CSM has to fill the managing forms enumerated in the beginning of this chapter and common to every RDI project at Bluepharma, which are accessible through the EnnovDoc (the company's documental system). They should be updated during the execution of the CT. I had the opportunity to collaborate in the planning of Bioequivalence clinical trials, helping completing those forms. Below is an explanation of each one and their main purpose.

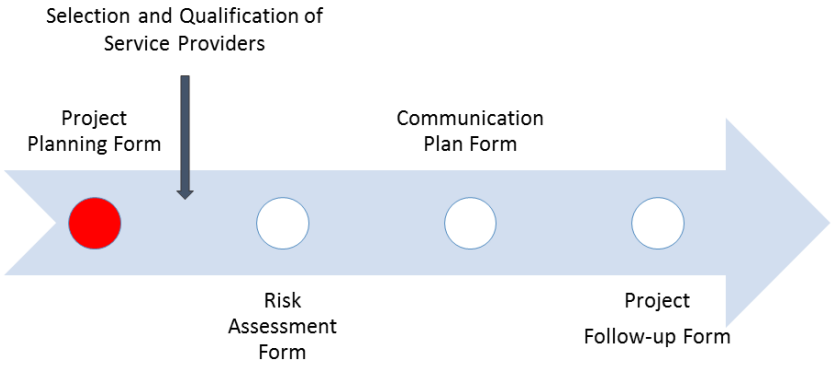

Figure 16 **– Process of planning phase I Clinical Trials at Bluepharma, Step 1: Project Planning Form**

The first form to be filled for the preparation of a clinical trial is the "Project Planning Form". In this form, the CSM:

- Describes the project and its timelines;
- Defines the main objectives, the project team and the necessary resources (human resources, costs…);
- Defines the type of monitoring activities that must be performed and their frequency.

The project planning helps to identify the company's needs: it clearly identifies all the persons involved on the project and their responsibilities, essential to perform an efficient management.
The internal project team or key persons involved in clinical trials at Bluepharma (in addition to the CSM) and their main functions, are enumerated in Table 3, below.

***Table 3* - Internal key players and their roles in a clinical trial sponsored by Bluepharma**

Head of Business and Product Development	• Responsible for the decision of which trials will be sponsored by Bluepharma and for negotiations and contracts with subcontractors and interested parties; • Responsible for the approval of all monitoring and audit reports.
Drug Safety Manager /Qualified Person for Pharmacovigilance (QPPV)	• Responsible for the safety information included in contract agreements between Bluepharma and the CRO (and/or Interested Parties), Study Protocol and its amendments and Final Study Report.
Phase I and II Project Manager	• Project manager for the phases I and II, before clinical trial phase of project (phase III). It has responsibilities related with the IMP.
Regulatory Affairs Manager	• Responsible for the preparation of regulatory documentation (IMPD and CTA, if applicable).
Galenical Development Manager	• Responsible for the IMP labelling, packaging, retention samples, shipment and for the recalls and IMP destruction.
Qualified Person (QP) / Product Quality & Compliance Department	• Responsible for the product compliance and for the releasing of the IMP.
Analytical & Galenical Development /Quality Control Unit	• Responsible for the analytical results certificate of the reference product, and for the release certificate of the test product.
Planning & Production Department	• Responsible for the production of the IMP and packaging of pilot batches.
Quality Management Department	• Responsible for the selection of the external auditors, for the revision of the contract agreements between Bluepharma and external auditors and for the evaluation of auditing plan and reports; • Responsible for issuing quality related declarations necessary for the shipment of IMP to the clinical phase.

When external resources are required, they are identified in this first step in order to be selected and subcontracted (Figure 18).

4.1.1. Selection and qualification of Service Providers

Bluepharma, as a sponsor, can subcontract part of the activities regarding the preparation and conduction of the CT to qualified service providers. However, the ultimate responsibility for the sponsor-related duties always resides with Bluepharma. As such, outsourced service providers and their personnel must be qualified and commit to comply with the regulatory requirements and with the GCPs.

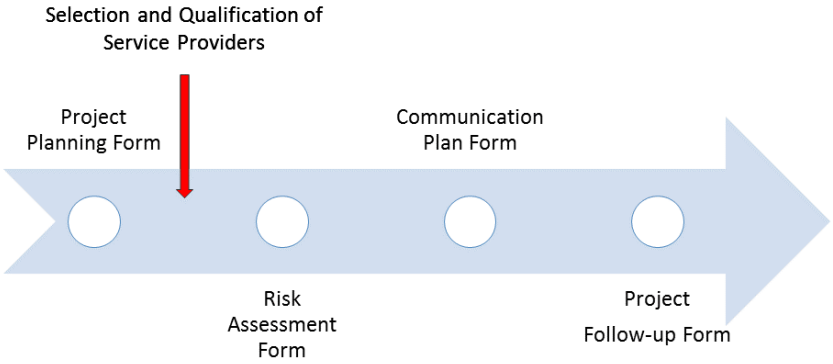

Figure 17 **- Process of planning phase I Clinical Trials at Bluepharma, Step 2: Selection and Qualification of Service Providers**

The CSM is responsible for the identification, evaluation and selection of qualified service providers.

The selection of a service provider by the CSM is based on a "Service Provider Evaluation Checklist", which has several evaluation criteria to demonstrate the ability of the service provider to perform the requested service, such as:

- ***The service status:*** expertise, geographic location, market reputation, etc.;
- ***The quality of the service provider:*** regulatory compliance, quality management system, SOPs, audit and inspection reports from Competent Authorities or other sponsors…;
- ***Human resources:*** availability, qualifications (assessed by CVs and years of experience);
- ***Adequacy of facilities and equipment***.

Bluepharma's Head of Business and Product Development signs the contract agreement between Bluepharma and the service provider, which include, in written, the responsibilities of both

parties, confidentiality clauses, timelines for the service, total amount to be paid and payment terms.

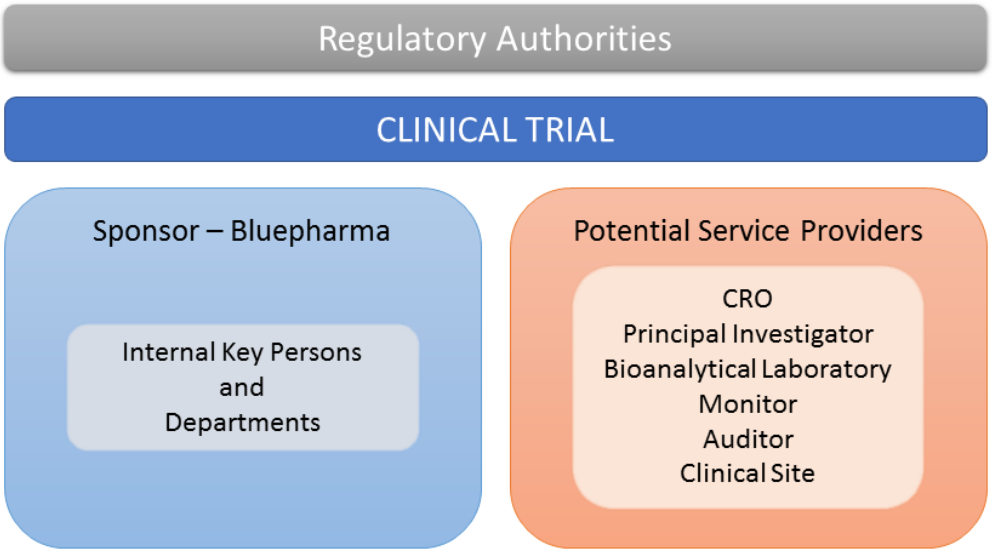

***Figure 18*- Potential Service Providers at Bluepharma**

Due to the fact that Bluepharma does not have the facilities nor the clinical team required for conducting clinical trials, a CRO and a clinical site must be subcontracted.

For some projects, Bluepharma or its clients/partner subcontract its subsidiary Blueclinical as CRO. This company has a phase I unit and all the human resources needed to perform the CT, including the investigators, nurses, data managers, pharmacists and medical writers. Blueclinical also performs quality control activities and subcontracts the Bioanalytical laboratory (which must be certified in GLP), offering an integrated service.

A monitor is also subcontracted by Bluepharma to perform the required monitoring visits regarding the quality control of clinical trial. The service providers are audited in a regular basis by Bluepharma.

4.1.2. Risk assessment

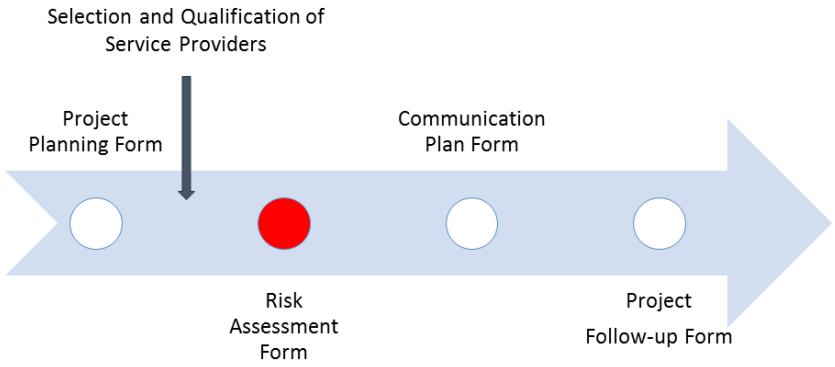

Figure 19 **- Process of planning phase I Clinical Trials at Bluepharma, Step 3: Risk Assessment Form**

After the initial project planning (and for each project), a risk analysis must be elaborated in order to identify, assess and mitigate the potential risks.

The Risk Assessment Form, another document to be completed by the CSM, includes:

- Identification of risks (e.g. related with IMP);
- Description of the potential failures associated with the risk;
- Evaluation of severity, probability and detection control in order to define the risk level;
- Measures to mitigate the risks;
- The responsible person for the mitigation each risk.

There are intrinsic risks to which a sponsor is exposed as financial risks resultant from the costs involved in the CT and legal risks, related with the lack of compliance with the legal requirements and with the GCPs (38). Other risks are inherent to the product characteristics and to the design of the CT (for example, when the pharmaceutical product is an HVDP) (39). For that reason, when designing a clinical trial, the characteristics of the product should be considered in the protocol in order to minimize the risk or take measures to control it. Some risks that can occur in a clinical trial and possible measures to mitigate them are enumerated in the Table 4.

Table 4 - **Examples of Sponsor's risks in phase I clinical trials and measures to mitigate them** (40)

	Risks	Measures to be taken
Before the Clinical Trial starts	• Inadequate communication plan for all the stakeholders (sponsor's personnel, CRO…) • Clinical site does not have the required features for the conduct of the CT • The CRO team does not have the experience required to perform the CT • Design of CT is not adequate for the objective or do not take into account the PK/PD characteristics of the drug (e.g. HVDP) • IMP circuit (storage, shipment) is not adequate according to the product specifications • Delays in shipment of the IMP • Delays in the CTA preparation • Delays in the CT approval • Inadequate contract terms with subcontractors (e.g. CRO) • Inadequate insurance agreement	• Communicate the timeline of the project with the team and CRO; • Weekly update of the project to the interested parties • Audit to the clinical site • Audit to the CRO • CT monitoring • Review of CVs of the principal investigator and of the clinical team • Review of protocol and other documents related with the CT • Datalogger during the shipment; records of humidity and temperature during storage • IMP sent with a considerable advance • Communicate deadlines with the team responsible for the CTA preparation • Review of written agreements • Check the insurance policy in order to assure that it covers all the aspects and risks for the clinical trial
During the clinical phase of the trial	• CRO does not fulfill with contract, GCPs and legal requirements • Inadequate safety reporting • Inadequate communication between clinical team and sponsor	• CT monitoring visits • Weekly update of Adverse Events to the sponsor
After the clinical phase of the trial	• Delays regarding the study results • Study outcomes (PK parameters, in the case of a bioequivalence) outside the limits for approval	• Inclusion of a sufficient number of participants in the clinical trial • Include in the contract the timings for the delivery of documents for review • Study design should be suitable to the product characteristics

4.1.3. Project plan communication

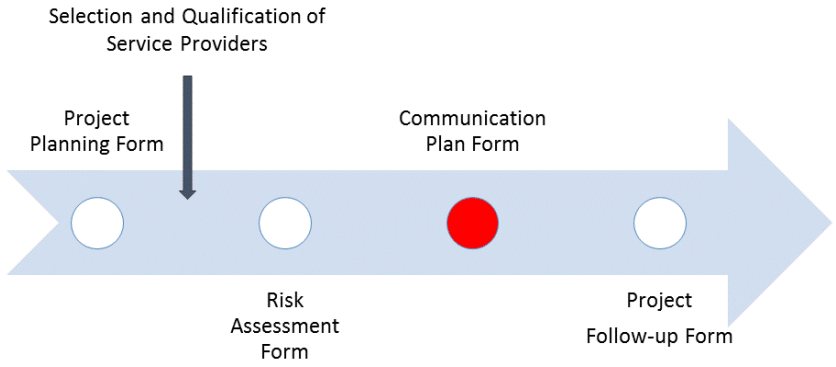

Figure 20 **- Process of planning phase I Clinical Trials at Bluepharma, Step 4: Communication Plan Form**

Communication between the team is an essential part of the process of project management since failures in communication from one (or more) individuals can lead to inefficiencies. All the team members must know when to communicate and to/from whom they have to disseminate or receive information.

Then, when planning a CT, it is necessary to prepare the communication plan, which includes: the information to be communicated, who is the target of the communication, when to communicate and the responsible person for undertaking that task. This matrix takes into account the risk analysis. As it can be seen in the table 4 "Examples of Sponsor's risks in phase I clinical trials and measures to mitigate them" there are several examples where an inadequate communication is critical for the performance of the project.

As stated before, at the beginning of the CT project and to guarantee that all the internal team members are informed, a kick-off meeting is schedule. After that, all the members of the team are aware of their responsibilities and then they have the obligation of updating the CSM about their tasks (e.g. production and packing of IMP, conclusion of IMPD, revision of the necessary documentation for the submission of CTA, IMP shipment). Any delay has to be communicated as soon as possible in order to minimize the impact in the activities to be performed by other members of the team or the need to reschedule the timelines.

4.1.4. Project follow-up

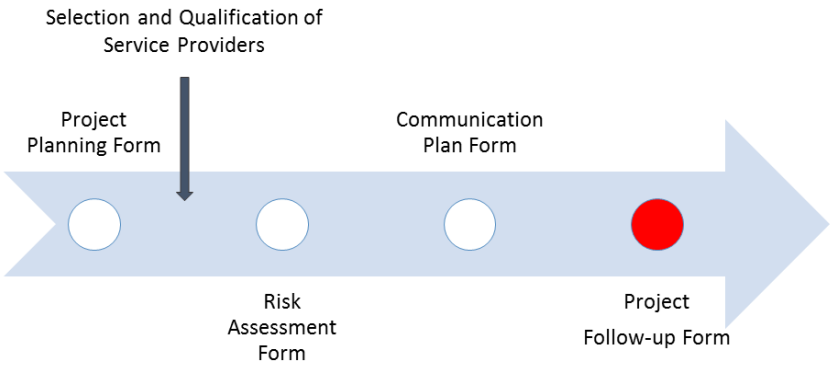

Figure 21 **- Process of planning phase I Clinical Trials at Bluepharma, Step 5: Project Follow-up Form**

The CSM needs to follow-up the project's execution to ensure the achievement of the expected outcomes. For that reason, the CSM must control the possible deviations from the original plan. Then, in the document "Project follow-up", the CSM states the main CT activities/milestones and their timelines, since the start of the CT until its close-out. During the execution, the CSM updates this document with the status of each activity. If there is any deviation, the CSM has to foresee the impact in the subsequent tasks and disseminate that knowledge, informing the team. Some examples of the activities to be follow-up during a CT project are: revision and approval of the documentation for the clinical trial submission, preparation of the documents for IMP shipment, the subject's screening and dosing, the results of bioanalytical analysis and the reception of the clinical study report for revision.

These activities are related with the main steps of the project (because there are the critical steps), enumerated in the Figure 17 "Process if conduction a Clinical Trial Project at Bluepharma and internal and external parties involved". This document is an excellent tool for CTs management.

During the internship I had the opportunity to fill these forms (project plan, communication plan, risk analysis and project follow-up).

4.2. Documentation review and approval for Clinical Trial Application

In Portugal, clinical trials must be submitted for approval to Infarmed, CEIC and CNPD. When submitting a clinical trial, a relevant number of documents are necessary. At Bluepharma, some of them are prepared by the company, other by the CRO and then reviewed and approved by Bluepharma. The documents to be prepared are summarized in the Table 5.

Table 5 **- Documents to be prepared for the submission of a Clinical Trial Application**

Documents	**Prepared and/or reviewed by:**		**To be submitted to:**		
	Bluepharma	**CRO**	**Infarmed**	**CEIC**	**CNPD**
Clinical Trial Protocol (CTP)	✓	✓	✓	✓	
IMPs Labels	✓		✓	✓	
Financial Agreement	✓	✓	✓	✓	
Letter of authorization (sponsor → CRO)	✓	✓	✓	✓	
Synopsis of protocol		✓		✓	✓
Informed Consent Form (ICF)	✓	✓	✓	✓	✓
CRF (template)		✓		✓	✓
Investigators Brochure		✓	✓	✓	
SmPC (reference product)	Send by the sponsor to CRO		✓	✓	
Investigational Medicinal Product Dossier (IMPD)	✓		✓	✓	
EudraCT number		✓	✓	✓	✓
XML File	✓	✓	✓	✓	
Insurance Agreement		✓	✓	✓	
Cover letter		✓	✓	✓	
Proof of fee payment		✓			
List of competent authorities		✓	✓	✓	

Ethics Commission authorization		✓	✓		
Investigators CVs		✓	✓	✓	
Volunteers compensation		✓		✓	
Investigators payment		✓		✓	
Active clinical trials with the same IMP		✓	✓	✓	
Ethics evaluation by principal investigator		✓			
Site conditions		✓		✓	

The documents review is performed by persons of different departments, according to the responsibilities assigned in the project planning form. The review is performed in order to ensure that documents comply with the guidelines and legal requirements. I had the opportunity to collaborate in the review of several CTPs and ICFs of BEs clinical trials conducted by different CROs.

4.3. Investigational Medicinal Product (IMP) circuit

Bluepharma is responsible for the production of the IMP and for the IMP circuit. IMPs must be manufactured (which includes not only the production but also the packaging and labeling), stored and distributed according to Good Manufacturing Practices (GMPs). Eudralex volume 4, in its annex 13, defines the GMPs related to IMPs. Other applicable legislation is the Law no 21/2014 and the ICH guideline E6 (R1).

As shown in Figure 22, GMPs ensure:

- That IMP complies with the specifications;
- That batches are consistent among them and that any change is documented, justified and can be verified;
- IMP traceability;
- That Clinical trial subjects are not placed at risk.

Each operation related to the manufacture and the circuit should have written procedures.

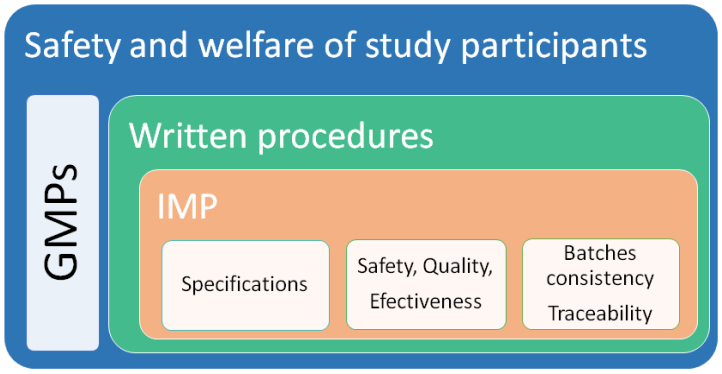

Figure 22 **– Objectives of GMP's compliance in clinical trials**

Below, in Figure 23, there is a scheme of the IMP circuit at Bluepharma:

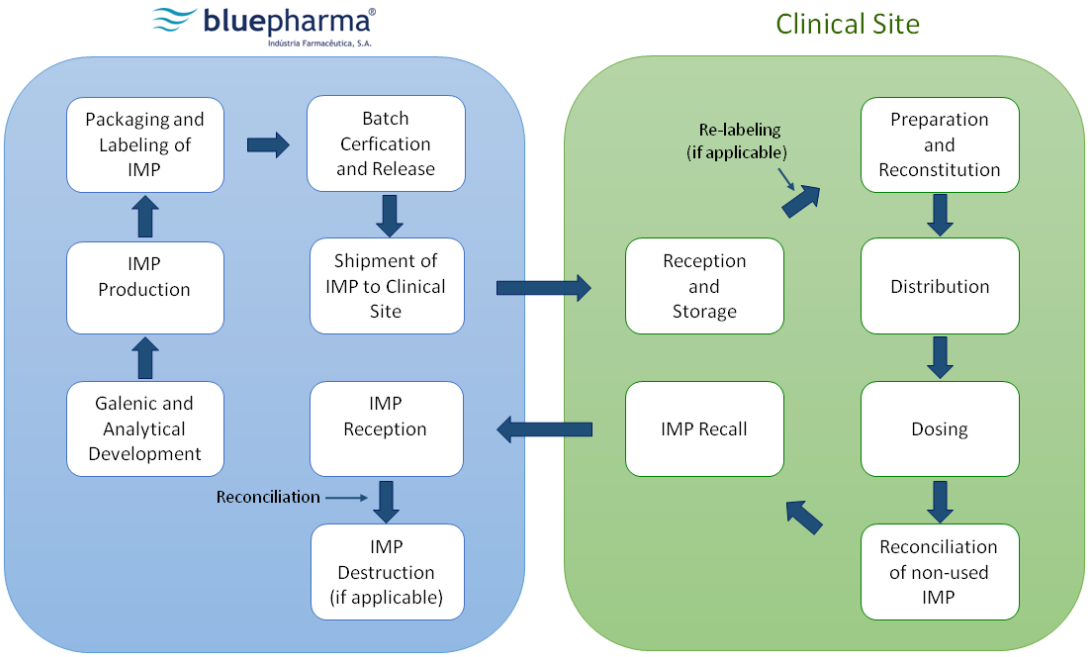

Figure 23 **- IMP circuit for phase I clinical trials sponsored by Bluepharma**

The amount of IMPs required to a clinical trial is calculated according to the number of subjects to be enrolled in the Clinical Trial. Bluepharma supplies both the test and the reference product for BE clinical trials.

Packaging and labeling

The packaging of the IMP for phase I studies is performed by Bluepharma but the individualization of the IMPs for dosing is normally performed at clinical site by the responsible pharmacist or under its supervision. Nevertheless, if necessary, Bluepharma as the necessary procedures in force to perform this task internally. Procedures for packaging and labeling must be in place. At Bluepharma, the Galenical Development Manager is usually responsible for the review and approval of the labels for dosing.

The following contents of the IMP label are described on the Annex 13 of Eudralex volume 4:

- Sponsor, CRO and PI (principal investigator) information: name, address and telephone number
- IMP information: pharmaceutical form, route of administration, number of units , name and dose (unblinded studies, such as BE),
- Study code;
- Clinical site;
- Batch number;
- Subject number;
- Instructions of use;
- Conditions of storage;
- Expiration date (month/year);
- "For clinical trial use only";
- "Keep out of reach of children" (not applicable for BE Clinical trials, because the product is not taken at subject's home, but at clinical site).

The language of the label must be the language of the country where the CT will be performed.

IMP Samples retention

There are two types of samples of the finished product to be retained:

- ***Reference samples:***
    - Only analyzed if necessary;

- Shall be in such amount which allows analytical control tests to be carried out for at least 2 times;
- Should be retained for 2 years after the trial.

- ***Retention Samples:***
  - Made for each packaging cycle/test period;
  - For the purpose of identification of IMP in the case of inconsistent experimental results.

At Bluepharma, the Galenical Development Manager is responsible for the samples storage. The documentation relating to each batch should be stored for 2 years after the completion of the CT. According to the results from stability studies, Bluepharma defines the IMP storage conditions (temperature, protection from light ...) and the expiration date.

Batch certification and release

The Qualified Person (QP), which is, at Bluepharma, the Head of the QP&C Department, certifies all the documentation related to the IMPs and issues the batch release certificate. The batch release certificate has to be kept in the Trial Master File (TMF) (41).

Shipping to clinical site

The IMPs shipment to the clinical site is Bluepharma's responsibility and can not be performed before the clinical trial approval for competent authorities not even before the batch certification by the QP. To ensure the transport conditions, a data logger must be included in the package. The records related to the shipment are maintained in the Trial Master File.

After the shipment, the data produced by the datalogger is evaluated by Bluepharma's QP&C department to ensure the shipment conditions and that the IMP has can be administered to the subjects. If there is a value outside the specifications defined by the sponsor, an assessment of the impact in the quality of the product has to be performed by Bluepharma's QP&C department. After the clinical phase, if the returned IMP is destructed, the destruction certificate will be archived in the TMF.

During the internship I made a research regarding the legal requirements for the IMP circuit and the requirements for IMPs shipment through European countries.

4.4. Clinical Phase

The procedures related with the clinical phase are performed by the subcontracted CRO/clinical site. Nevertheless, during this phase, the CSM maintains close contact with the CRO in order to follow-up of the conduction of the trial (if there were any adverse reactions, withdraws, etc.).
For quality control purposes, a subcontracted study monitor performs several monitoring visits during the clinical phase. Usually, the visits below are performed for a bioequivalence clinical trial:

- ***Site initiation visit:*** performed before the screening of the first subject, with the aim of verifying if all required documents and materials are in place to IMPs administration;
- ***Site monitoring visit:*** performed during the subjects dosing, to verify the compliance to the protocol and SOPs, to review documents (e.g. SAEs reporting) and confirm the IMP supplies.
- ***Site close-out visit:*** schedule with the site staff after the study report signature. It aims to identify missing documents (e.g. in the TMF) or the need of shipping the unused IMP/study related materials.

After each visit, the Study Monitor prepares a monitoring report to be sent and review by Bluepharma. During my internship I had the opportunity to read several monitoring visit reports.

4.5. After clinical phase

Clinical Study Report (CSR)

After the end of the clinical phase, the bioanalytical analysis of the samples is performed by a GLP certified laboratory and their results are statistically analyzed. After that, a medical writer (usually from the CRO) elaborates the clinical study report. As sponsor, Bluepharma is the final responsible for all the information stated in the clinical study report. For that reason and according to Bluepharma's internal procedures, a multidisciplinary team has to perform a thorough revision of that document for quality purposes.
I collaborated in the revision of clinical study reports prepared by European and overseas CROs. My revision was carefully performed taking into account the topics below:

- The procedures stated in the CSR must comply with the protocol;

- The data registered in the CSR must match with those in CSR appendices;
- Special attention to adverse events, protocol deviations, drop outs or subject's withdraw, compliance with inclusion and exclusion criteria.

Sometimes, the revision of a sampling number of Case Report Forms (which is the form, developed according to the clinical trial protocol, where clinical site personnel collect the data of each participant in CT during the clinical phase) is needed. I participated in the review of Case Report Forms of subjects that participated in a Bioequivalence trial sponsored by Bluepharma.

Even though the review of CSR and CRFs depends on the characteristics of the study (design, risk associated with IMP…), the final goal of reviewing documents, for a sponsor, is always to verify the full compliance with GCPs and other applicable regulations.

Trial Master File (TMF) reception and storage

Clinical trial related documents must be accessible for monitoring and auditing by the sponsor or regulatory authorities.

At Bluepharma, after the completion of CT the TMF is kept by the CSM in the archive, which is an area where the necessary humidity and temperature conditions for documents archiving are guaranteed.

EudraCT register

European Commission and regulatory authorities such as EMA, FDA and other organizations as World Health Organization (WHO), published a number of policies, regulations and statements regarding the transparency of data, which affects the data resultant of clinical trials (Regulation EC No 1049/2001, EMA Policy/0043 of 30 November 2010, and WHO Statement on Public Disclosure of Clinical Trials Results). There is a special concern to the disclosing of clinical trials results (42).

Since 21 July 2014, is mandatory for sponsors, as Bluepharma, to post the clinical trials results until one year after the completion of the clinical trial. For that purpose, a summary of the CT results is submitted on the EudraCT website. That information will be made publicly available through the EU Clinical Trials Register website (42) (43) (44).

To submit the results, the CT sponsor has to register in the EudraCT website and then insert the necessary information of each clinical trial regardless of its negative or positive results.

During my internship, I had the opportunity to submit the results of some clinical trials sponsored by Bluepharma in the EudraCT website.

5. Supporting the clinical research activities

5.1. Innovation Strategy: management of new ideas

As said in the introduction of this report, Bluepharma is a SME that manages its resources wisely aiming its sustainable growth.

As explained before, in the sequence of interfaces management, the Norm NP 4457 mentions that all the ideas should be managed. During NP 4457:2007 implementation, Bluepharma's Research Department developed a method for the management of new ideas and opportunities and elaborated a SOP for Ideas Management. It defines the objectives, the team involved and all the process, since the generation of ideas until the selection of the best ones to go forward as projects. Below, the Figure 24 represents a scheme of Bluepharma's internal process for management of new ideas:

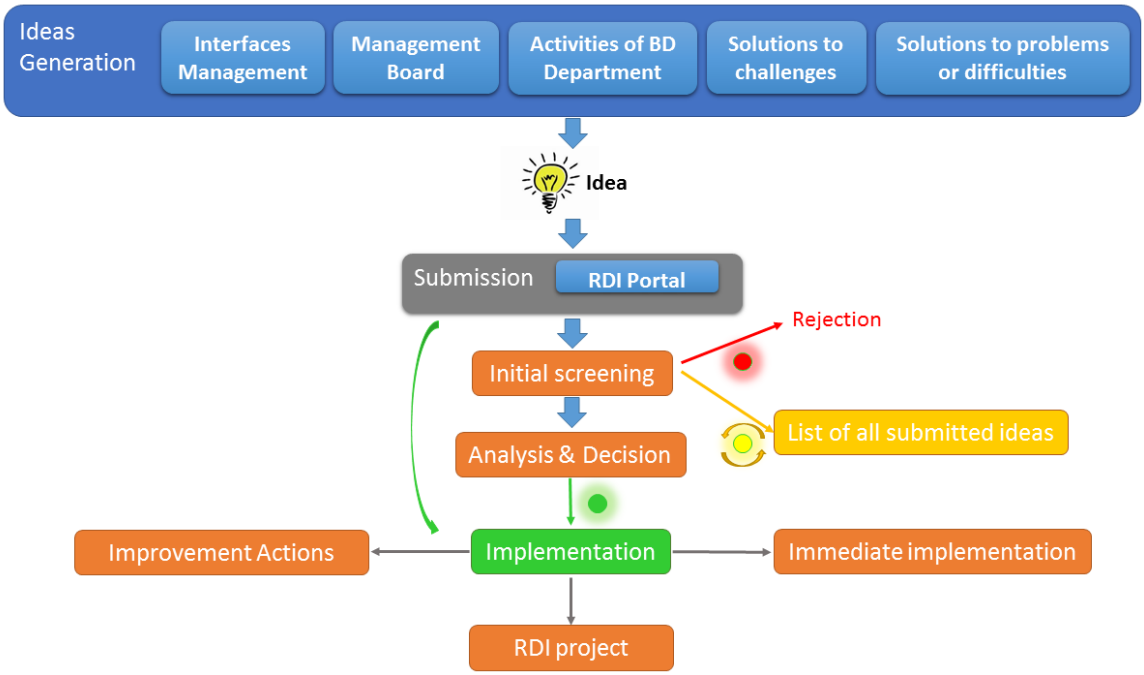

***Figure 24*- Ideas Management at Bluepharma**

Internally, there are several participants in these activities:

- ***RDI Director/ Board of the company*****:** responsible for the final decision regarding the implementation of an idea.
- ***Ideas Manager*****:** responsible for the compliance with the SOP for Ideas Management and to promote the creativity within the company, perform the initial screening of ideas and manage the "List of all submitted ideas".
- ***Idea Analysis Committee*****:** after the initial screening of an idea, this committee performs its analysis, according to the criteria that will be described below.
- ***All employees:*** all the persons inside the company should be proactive, creative and seek new ideas.

As can be seen in the figure above, the source of one idea at Bluepharma can be:

- ***Interfaces management*****:** the activities related with the interfaces management allow the identification of potential opportunities, by monitoring the external environment of the company. These activities are performed systematically by several members of the company, usually seniors, who can understand the impact of the information for the strategy of the company. The persons involved in gathering the information are also responsible for the dissemination of the knowledge gained to the persons or departments where it could be important.
- ***Management Board*****:** new ideas can emerge from the contacts between the members of the management board and clients, universities, independent researchers, participation in fairs, etc.
- ***Activities of Business Development Department*****:** arising from business opportunities, identified when the contact with clients and participations in fairs.
- ***A solution to a challenge that the board of the company proposes to all collaborators*****:** twice a year the management team asks all collaborators for solutions for critical

> *"There is a general consensus, looking at the pipeline, that the number of new product approvals each year will remain the same for a while. Those in the drug discovery business have picked all the low-hanging fruit. Now they have to reach out for the fruit at the top of the tree, but the latter isn't always quite high enough."*
>
> Thomas Lonngren, Executive Director of the EMA, quoted by Deloitte, March 2009

problems of the organization. The authors (a person or a group of persons) of the best idea will receive a premium.

- ***Solution to problems and/or difficulties*:** this can be identified by any employee or by the management board.

Submission of new ideas

To facilitate the submission of ideas by all collaborators, an RDI Portal, accessible through the Internal Portal of Bluepharma (an internet platform), was implemented. The system is intuitive and allows not only the ideas submission but also their status and follow-up by the author. All collaborators of Bluepharma can access the RDI Portal to submit ideas. This Portal is also used for the monitoring activities regarding the interfaces management.

Analysis of new ideas

All the ideas submitted pass through an initial assessment, carried out by the Ideas Manager. The objective is to carry out a previous selection of the ideas that suit to the objectives or the needs of the company. All the ideas that pass this initial sieve will be analyzed by a group of collaborators, the Analysis Committee, chosen by the Ideas Manager and by the RDI Director.

The only objectively and reproducible approach to evaluate several (and different) ideas and to be certain that the better ones are chosen, is using the same method for all of them. For that reason, at Bluepharma, all Analysis Committees evaluate ideas in a defined timeline and in a defined form, depending on the type of idea (Table 6):

***Table 6* - Contents of the forms for ideas evaluation**

Form "Analysis and Classification of Product Ideas"	Form "Analysis and Classification of Other Ideas"
•Description •Product Information •Reference product information •Target product information •Drug substance information •Clinical trials information •Market data •Competition •Intellectual property landscape •Regulatory environment •Main project activities and timelines •Cost structure and price estimation •SWOT analysis •Risk assessment	•Description •Objective •Competitors •Financial data •Intellectual property landscape •Regulatory environment •Main Project Activities and Timelines •SWOT analysis •Risk assessment

To perform this analysis is necessary an extensive research in scientific and non-scientific databases. This information must have quality, be objective and reliable. I had the opportunity to contribute for the assessment procedure of some new product ideas. For that, I made bibliographic research on many resources: clinical trials databases, scientific articles, websites of regulatory authorities (EMA, FDA…) or other entities (WHO, European Commission…), websites of other pharmaceutical companies and/or stakeholders, etc.

At Bluepharma, the Research and the Business Development Departments meet in order to discuss new ideas and projects. I had the opportunity to be in one of those meetings, which aim to discuss the future of two ideas assessed before. The ideas were presented one after the other in a PowerPoint by the members of the Analysis Committee, who explained to the presents the rationale and the data gathered.

Completing this form gives a general perspective of the idea: the strengths and weaknesses, the several phases, the resources needed, the economic data and the foreseen return of investment. When completed the form is send to the Board of the company to support a go/ no-go decision.

Decision about new ideas

If the decision of the board of the company is to going forward with the idea and implements the new idea, the idea is categorize as:

- RDI project;
- Improvement action;
- Immediate implementation.

If the decision is to not implement the idea, it will not be discarded and will always be available for future consideration.

5.2. Scientific information

The importance of the databases

The internet is a large pool of information and is the most used tool for research. It is important to know how to gather the best information. There are many available resources, scientific or not, used to take important decisions, as those described before.

At Bluepharma, in addition to the research in scientific websites and databases, I was taught how to perform a research in Cortellis and Newport Thomson Reuters databases.
Newport database has global information and is used for research information about consumption of API, development and licensing of medicines, competitors, and patents (45).
The Cortellis database is used by life science professionals and it has information on the development of products, from pre-clinical trials to after the product's marketing, sales information and forecasts. This database allows to filter the information and to select only the interesting one, which is presented in a table that can be exported to an excel document. After exporting the table, the data need to be analyzed, in order to filter the fields according to the specific objectives of the research (46).
The information collected on these databases is important because it helps to identify and evaluate market opportunities for new products and to identify the competitors.
For patent search, there is a website of interest, the "www.wipo.int", which is a free platform of information about intellectual property.

6. Training courses

During the internship I had the opportunity to attend to several internal training courses that can be divided according to the main objectives. Some provided information about the mission and vision of Bluepharma and how they are achieved, and other about the main activities of the company. Those are important for the integration of new collaborators; and other are specific of the work field and provided the necessary tools to perform the daily activities.
Below are the training courses that I attended during the internship.

Bluepharma's Initial Presentation

The process of integration new collaborators starts with an initial visit at Bluepharma's facilities. The initial presentation of the company included:

- ***A presentation of Bluepharma*:** with the evolution of the company, mission, vision, strategic vectors and certifications;
- ***Presentation of Research Department*:** about its evolution, mission, vision and team;
- *Quality management systems*: Integrated Quality Management System, GMP, ISO 9001, ISO 14001, OHSAS 18001, EMAS;
- ***Documental System*:** EnnovDoc;
- ***Bluepharma's Internal Portal*:** Sharepoint;
- ***Policy for responsible use of IT resources***.

Specific Training

- ***Basic Research Tools (Scientific and No Scientific):*** use of databases, Cortellis and Newport;
- ***RDI management*:** NP 4457, project management and improvement actions;
- ***RDI: ideas management and RDI Portal***;
- ***Regulatory affairs***;
- ***Pharmacovigilance***;
- ***Lifecycle of medicines.***

7. Discussion

In order to better summarize the experience and understanding acquired during the internship, I divided this discussion in two parts:

1. The critical points to consider when sponsoring clinical trials;
2. The importance of innovation strategy in the pharmaceutical industry.

Sponsoring clinical trials

Bluepharma's mission is to deliver quality and affordable solutions for patients, namely generic medicines. The development of a new generic medicine relies on the development of a product that has to prove its bioequivalence to its reference product. For that, a bioequivalence trial must be performed and Bluepharma, as a sponsor, takes the full responsibility for the CT. During my internship I realized that the critical points to consider when sponsoring clinical trials are:

- ***Perform an efficient clinical trial management:*** this includes the planning of the CT, the follow-up of the timelines and a good internal and external communication (CRO and partners, if applicable). A good alignment between all the members of the team is necessary. All persons must be aware of the follow-up of the project, since it is necessary to comply with the deadlines (e.g. CT submission) in order to achieve the project objectives. As in any other project, the risk analysis of all the steps of the CT is important for its success because it allows the identification of the factors and activities that can be critical for the outcome achievement.
- ***Take into account the drug product characteristics:*** To achieve a positive result in the BE clinical trial, the characteristics of the drug product are critical. The majority of the molecules today present chemical characteristics (e.g. HVDP) that require a careful consideration when planning the bioequivalence clinical trial: the design, the statistical approach and the position of the regulatory authorities in the matter. The risk of these projects is greater and has to be considered by the sponsor.
- ***Perform clinical trials in emerging countries (e.g. India):*** another challenge to a clinical trial's sponsor is when the clinical trial is performed by a CRO belonging to emerging countries. This presupposes additional careful in the management of the clinical trial and

in the review of the documentation. The quality control and assurance and the communication are more demanding, but essential to ensure that service providers outsourced comply with the GCPs and legal requirements. Non-compliance could mean the inability to be a sponsor and exposes the company to a great risk. In the clinical investigation field, the selection of service providers requires careful consideration.

The importance of Innovation Strategy

The pharmaceutical industry is dominated by large companies ("big pharmas"), acting globally, with internal capabilities, and high investments in R&D.

Companies need promoting their sustained growth and understand how and where to innovate. In general terms, innovate is bringing a solution to existing problems, which could have several origins: they could be a market need or an internal need (within the company). Hence, in an organization, we can innovate not only in new products, but also in management processes or implementing new business models.

It is possible to achieve this goal by looking and monitoring the external environment in which the company is inserted. Not less important is the deep knowledge of the internal capacities of the company. These principles are those of the interfaces management. Summarizing, is essential to get knowledge about:

- Which are the competitors, and what products or services they are developing;
- What are the market's unmet medical needs;
- What are the regulatory updates and the last directives;
- With which companies, institutions and universities partnerships can be established;

Also, is important to promote creativity and critical thinking within the company.

These activities allow the identification of opportunities and threats and could be generator of new ideas. However, while having several potential projects in hand, it is necessary to choose which ideas have greater potential to be implemented in the company. The evaluation of different ideas, through a method that compares all them makes possible to know how they are aligned with the company's strategy and allows an easier go/no go decision by the management board of the company. Furthermore, the evaluation of the idea also allows the knowledge of:

- The idea related risks, strengths and weaknesses;
- What are the several phases of the project and how they can be executed;
- The resources and capacities are needed to lead the project until the end;

- The knowledge of economic data about the product;
- The foreseen return of investment.

At Bluepharma, challenges can be viewed as development opportunities. Adding the know-how of management, to a good strategy and to the team effort, all the ingredients will be present to overcome the obstacles that appear.

Figure 25 **- Bluepharma's strategy overview**

8. Conclusion

During the internship at Bluepharma, it was possible for me to understand that the pharmaceutical industry as a highly regulated and competitive environment and has several challenges ahead. It was important to understand how growth in the pharmaceutical industry can be achieved. I acquired a practical knowledge regarding the compliance with the applicable regulations through an integrated quality management system.

Within the scope of the of RDI project's management, my experience in the process of ideas evaluation was very important to realize how the growth of a company can be sustained through the investment in research and innovation and how this could be achieved by the interfaces management, ideas management and opportunities assessment. The study of the SOPs and the access and filling of the forms for ideas evaluation (namely regarding the topics related with drug substance information and with clinical trials) were the main factors contributing for that knowledge. This activity implied an extensive research work about product's characteristics, guidelines and legislation.

Bluepharma is a SME with several departments and some of them comprise relatively large teams. In the field of the CT management and to perform a good management it is necessary to understand how the different departments interact with each other, which are the key persons and their main functions. Understanding the company's structure is critical. The initial training courses and the support I received from the Medical Affairs Unit team were important in this knowledge achievement, as well as the company's documents (SOPs) and filling the different forms regarding the management of the clinical trials.

It was possible to understand how to manage bioequivalence clinical trials, the difficulties to face in order to ensure the compliance with GCPs and with the regulations. The CT documentation review allowed me to understand all the work needed to guarantee an efficient quality control. The researches carried out regarding the IMP circuit, the CT's documentation archive and the HVDP also helped me to understand the processes and the internal procedures.

It can be concluded that this training experience at Bluepharma was for me a great opportunity to meet the work in a pharmaceutical industry, understand its environment and gain experience in the field of clinical trials. I realized that this experience has enriched me: I am aware that I grew up and that the commitment of the people, their dedication, and the importance of performing a work of excellence are something that will follow me in my future professional life.

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